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Shape linear peptides into rigid rings: a sp^3 C–H arylation approach to cyclophane-braced peptide macrocycles

Yuankun Dao & Suwei Dong*

State Key Laboratory of Natural and Biomimetic Drugs, and Department of Chemical Biology, School of Pharmaceutical Sciences, Peking University, Beijing 100191, China

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Peptide-based therapeutics have attracted increasing attention due to their unique properties in comparison to small molecule drugs and recombinant biologics [1]. With moderate size and suitable surface area, peptides possess enormous potential in drug discovery for their promising capabilities of intercepting protein-protein interactions (PPIs), which is extremely difficult to be accomplished using small molecule compounds [2]. However, the biological instability and poor membrane permeability of peptides have significantly compromised their value as drug candidates or therapeutics. Macrocyclization is a widely applied strategy to overcome the disadvantages of linear peptides, as many naturally-occurring peptide macrocycles display dramatically increased metabolic stability and membrane permeability. Currently most of the approaches utilize a single linkage of amide (or disulfide, or thioether, etc.) bond to effect the cyclization, which often lead to flexible three-dimensional structures and less stable macrocycles. In contrast, several types of natural products, such as cyclotides with multiple disulfides (e.g., Kalata B1, Figure 1(a)), and cyclophane framework-containing cyclic peptides (e.g., vancomycin), can adopt constrained conformations that result in much higher stability than that of the linear peptides. Efforts have thus been endeavored to develop efficient ways to prepare these stable macrocyclic structures for chemical biological and medicinal studies. While quite a number of methods can be listed for macrocyclizing peptides in an efficient manner, forming C–C linkages in the cyclization event, directly connecting the amino acid side chains of the corresponding linear precursors, remains a formidable challenge due to the rigidity of usually highly constrained structures.

Recently, Professor Chen and collaborators [3] have developed a robust and highly efficient strategy for constructing cyclophane-braced peptide macrocycles through an intramolecular arylation of unactivated $C(sp^3)$–H bond (Figure 1(b)), drawing inspirations from the enzymatically controlled formation of natural macrocycles, where the cyclization proceeds through the functionalization of the C–H bonds on side chains of the amino acid residues bearing aromatic and/or aliphatic groups. On the basis of their previous success in using 8-aminoquinoline (AQ) and 5-methoxyl-8-aminoquinoline (MQ) in palladium (Pd)-catalyzed sp^3 C–H arylation reactions [4,5], Chen *et al*. installed the auxiliary on the C-terminus of the linear peptides, and utilized $Pd(OAc)_2$ as catalyst to facilitate a selective C–H activation at the β-position of the carboxamides. Consequently, iodinated Phe, Tyr and Trp, or iodoaryl-modified Ser, Glu and Lys, could then react in a "cross-coupled" manner to construct the C(alkyl)–C(aryl) bond, thus leading to the formation of cyclophane-containing cyclic peptides. Evaluation of a wide variety of linear peptide substrates has proven that this protocol is highly efficient, generally applicable, and operationally simple, affording macrocycles

*Corresponding author (email: dongs@hsc.pku.edu.cn)

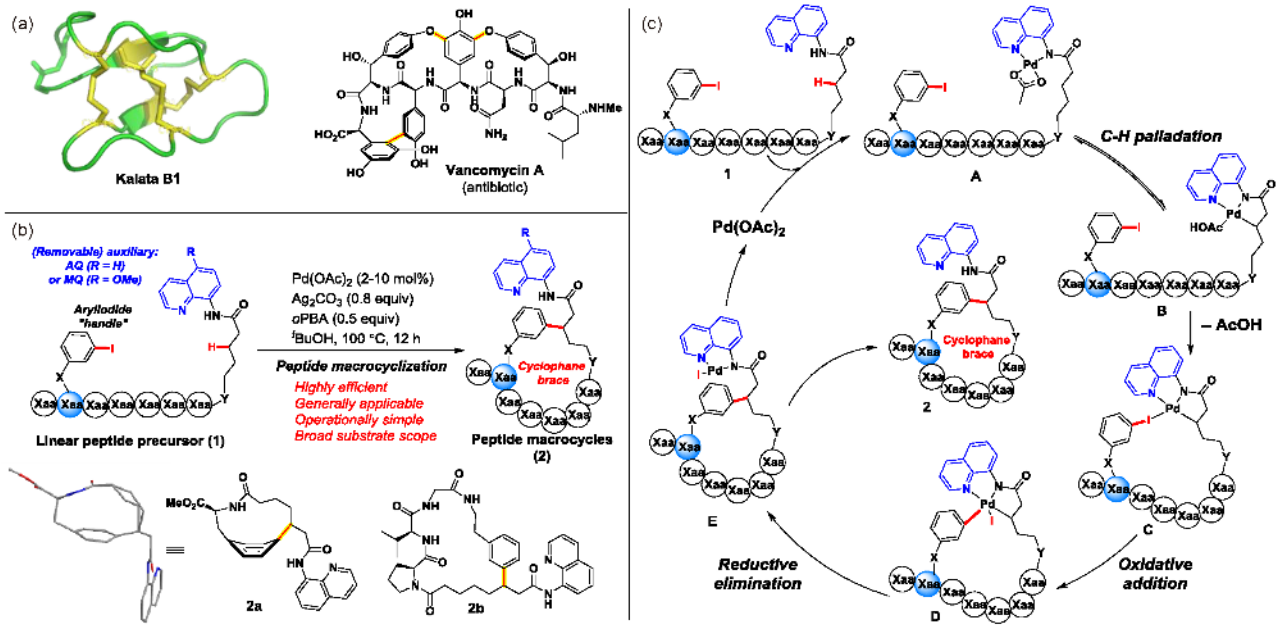

Figure 1 (a) Left: 3D structure of cyclotide Kalata B1 containing three disulfides (colored in yellow) in a ribbon presentation; right: chemical structure of and cyclophane framework-containing macrocyclic natural product vancomycin A. (b) Macrocyclization of peptides using palladium-catalyzed C(sp^3)–H arylation strategy. (c) Proposed mechanism of palladium-catalyzed C(sp^3)–H arylation for the synthesis of cyclophane-braced peptide macrocycles (color online).

with controllable size ranging from small (11-membered) to large (37-membered) ones. Remarkably, highly strained ring structures (e.g., **2a**, Figure 1(b)), could be efficiently generated using this method. The cyclophane brace within the macrocycle was further confirmed by X-ray crystallography, revealing a distinct rigid loop-type three dimensional structure. Moreover, in order to get an insight of the mechanism involved in this cyclization reaction (Figure 1(c)), Chen and coworkers conducted density functional theory (DFT) calculations, which suggest that the success of this challenging transformation may be largely attributed to the exothermicity of the palladacycle arylation, resulting an overall highly exergonic cyclization process. Further biological evaluation and membrane permeability test of the synthesized macrocyclic peptides revealed a number of compounds that with anti-cancer cytotoxicity and/or excellent permeability, demonstrating the potential of these synthetic macrocyclic peptides as lead compounds for drug discovery.

In summary, this highly efficient protocol developed by Chen *et al.* represents a remarkable success of applying C–H activation strategy to convert complex linear peptides to challenging constrained macrocycles, solving the long-standing issue of size- and composition-dependence in such events. This methodology should greatly accelerate the access to a diverse collection of novel macrocyclic structures, which should be of great value in the survey of promising lead compounds for the development of peptide-based therapeutics.

Conflict of interest The authors declare that they have no conflict of interest.

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